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Chinese herbal medicines for hypertriglyceridaemia

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ABSTRACT

Background

Hypertriglyceridaemia is associated with many diseases including atherosclerosis, diabetes, hypertension and chylomicronaemia. Chinese herbal medicines have been used for a long time as lipid-lowering agents.

Objectives

To assess the effects and safety of Chinese herbal medicines for hypertriglyceridaemia.

Search methods

We searched a number of databases including The Cochrane Library, MEDLINE, EMBASE and several Chinese databases (all until May 2012).

Selection criteria

Randomised controlled trials in participants with hypertriglyceridaemia comparing Chinese herbal medicines with placebo, no treatment, and pharmacological or non-pharmacological interventions.

Data collection and analysis

Two review authors independently extracted data and assessed the risk of bias. Any disagreement was resolved by discussion and a decision was achieved based on consensus. We assessed trials for risk of bias against key criteria: random sequence generation, allocation concealment, blinding of participants, incomplete outcome data, selective outcome reporting and other sources of bias.

Main results

We included three randomised trials with 170 participants. Ninety participants were randomised to the Chinese herbal medicines groups and 80 to the comparator groups with numbers ranging from 50 to 60 participants per trial. The duration of treatment varied from four to six weeks. All the included trials were conducted in China and published in Chinese. Overall, the risk of bias of included trials was unclear. There were no outcome data in any of the trials on death from any cause, cardiovascular or cerebrovascular events, health-related quality of life, or costs.

Three different herbal medicines, including Zhusuan Huoxue decoction, Huoxue Huayu Tongluo decoction, and Chushi Huayu decoction were evaluated. All three trials investigating Chinese herbal medicines treatment alone (two studies) or in combination with
gemfibrozil (one study) reported results on serum triglyceride (TG) in favour of the herbal treatment. We did not perform a meta-analysis due to significant clinical heterogeneity between the studies.

No relevant differences in adverse effects occurred and no serious adverse events were noted.

**Authors’ conclusions**

The present systematic review suggests that Chinese herbal medicines may have positive effects on hypertriglyceridaemia. The trials did not report serious adverse effects following Chinese herbal medicines treatment. However, based on an unclear risk of bias in included studies and lack of patient-important long-term outcomes, no definite conclusion could be reached.

**PLAIN LANGUAGE SUMMARY**

**Chinese herbal medicines for hypertriglyceridaemia**

Hypertriglyceridaemia is a condition characterised by increased blood levels of triglycerides, which constitute one of the blood lipid components. Hypertriglyceridaemia can be divided into primary and secondary types. Hypertriglyceridaemia is associated with many diseases including atherosclerosis, diabetes and hypertension.

To evaluate the effects of various herbal formulations (including single herbs, Chinese proprietary medicines, and mixtures of different herbs) for treating hypertriglyceridaemia, we examined all available randomised controlled trials of Chinese herbal medicines. We identified three studies lasting from four to six weeks and recruiting 170 participants with hypertriglyceridaemia. There were no data on death from any cause, cardiovascular or cerebrovascular events (such as heart attacks or strokes), health-related quality of life, or costs.

We found that Chinese herbal medicines used alone or in combination with lipid-lowering drugs or 'life style' changes may have positive effects on reducing the blood levels of triglycerides. No relevant differences in adverse effects occurred and no serious adverse events were noted.

On the basis of the current evidence, no definite conclusion is possible especially because of the unclear risk of bias in the included studies and lack of reporting on patient-important long-term outcomes.
**SUMMARY OF FINDINGS FOR THE MAIN COMPARISON**

Traditional Chinese herbal medicines compared with western medicine for hypertriglyceridaemia

**Patient or population:** participants with hypertriglyceridaemia  
**Settings:** not always specified  
**Intervention:** traditional Chinese herbal medicines  
**Comparison:** benzbromarone, gemfibrozil, fenofibrate

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>See comment</td>
<td>See comment</td>
<td>Not investigated</td>
</tr>
<tr>
<td>Cardiovascular or cerebrovascular events</td>
<td>See comment</td>
<td>See comment</td>
<td>Not investigated</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>See comment</td>
<td>See comment</td>
<td>No serious adverse events were reported in the three included studies</td>
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<tr>
<td>[follow-up: 4 to 6 weeks]</td>
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<tr>
<td>Health-related quality of life</td>
<td>See comment</td>
<td>See comment</td>
<td>Not investigated</td>
</tr>
<tr>
<td>Costs</td>
<td>See comment</td>
<td>See comment</td>
<td>Not investigated</td>
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<tr>
<td><strong>Serum triglyceride concentrations (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>[follow-up: 4 to 6 weeks]</td>
<td></td>
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<tr>
<td>a. Zhusuan Huoxue decoction + lifestyle intervention vs fenofibrate + lifestyle intervention</td>
<td>a. 60 (1)</td>
<td>⎟⊕⊕⊕⊕ very low*</td>
<td>a. Statistically significant higher triglyceride levels after Zhusuan Huoxue decoction</td>
</tr>
<tr>
<td>b. Huoxue Huayu tongluo decoction plus gemfibrozil vs gemfibrozil</td>
<td>b. 60 (1)</td>
<td></td>
<td>b. No statistically significant differences</td>
</tr>
<tr>
<td>c. Chushi Huayu decoction vs benzbromarone</td>
<td>c. 60 (1)</td>
<td></td>
<td>c. Statistically significant lower triglyceride levels after Chushi Huayu decoction</td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence  
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.  
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  
**Very low quality:** We are very uncertain about the estimate.

*Due to very serious indirectness, low number of studies and patients, and inconsistency of results
BACKGROUND

Description of the condition

Hypertriglyceridaemia (HTG) is a condition characterised by high blood levels of triglycerides, constituting one of the blood lipid components. Hypertriglyceridaemia can be divided into primary and secondary types. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) defined elevated triglycerides as 1.69 mmol/L (150 mg/dL) and higher (NCEP 2001). The Third National Health and Nutrition Examination Survey (NHANES) found that approximately 1.7% of thesample had HTG, equating to roughly 3.4 million Americans in the US, adults aged 20 years and older (Christian 2011). The participants with severe HTG tended to be men (75.3%), non-Hispanic whites (70.1%), and aged 40 to 59 years (58.5%) (Christian 2011). The prevalence of HTG was approximately 35% in men and 25% in women in US adults aged 20 years and older (NCEP 2001). The adjusted prevalence of HTG (above 1.70 mmol/L) among adults aged 18 years and older was reported to be 11.9% in China (Li 2005). The MONICA survey, carried out in three sub-districts in Jakarta in 1993 reported that the prevalence of HTG was 32.1% in males and 20.6% in females (WHO 2000).

Hypertriglyceridaemia is often associated with other lipid abnormalities and co-exists with other cardiac and vascular risk factors including the ‘metabolic syndrome’ (Li 2005; NCEP 2001). Elevated triglycerides often occur in parallel with high levels of cholesterol. While mild-to-moderate HTG is not usually associated with overt physical signs, lipoaemia retinialis and eruptive xanthomas have been associated with severe HTG which has also been associated with life-threatening acute pancreatitis (Kumar 2005; Martinez 2008). Hypertriglyceridaemia may be further associated with many diseases including atherosclerosis, diabetes, hypertension and chylomicronaemia syndrome (Anderson 2011; Chait 1992; Le 2007; Mota 2004; Zhang 2011). The relationship between HTG and atherosclerosis remains controversial. Meta-analyses of thousands of patients followed up for more than 10 years in prospective studies showed that a triglyceride elevation of 1 mmol/L (88.8 mg/dL) increased the risk of cardiovascular disease by 32% in men and 76% in women, independent of HDL-C levels (Hokanson 1996).

Adverse effects of the intervention

Herbal medicines used for lowering blood lipid levels have been associated with symptoms and signs including reduced appetite, nausea, abdominal discomfort, abdominal distension, diarrhoea, increased blood urea nitrogen (BUN) and hepatic dysfunction with isolated elevation of alanine-aminotransferase levels (ALT). No serious adverse effects have been reported (Liu J 2006; Liu 2008), and the safety profile of herbal medicines in long-term use has not been sufficiently assessed.

How the intervention might work

The mechanisms of action of herbal medicines in lowering blood triglycerides are largely unclear and may be complex; the small body of work in this area has been limited largely to animal experiments. Some potentially active ingredients from medicinal herbs have been identified. For example, purified Salvia miltiorrhiza extract as a farnesoid X receptor/liver X receptor alpha co-agonist has been shown to improve the lipid profiles in hyperlipidaemic rats (Ji 2008), and the mechanism of Daming capsule in lowering blood lipids may be related to the change of Cx43 (Xing 2007). However, the mechanisms of most herbal medicines for lowering triglycerides are not well defined.

Why it is important to do this review

Although there is evidence from randomised clinical trials (RCTs) that herbal medicines improve lipid profiles, the evidence is by
no means conclusive. One review on Chinese red yeast rice for primary hyperlipidaemia inferred short-term beneficial effects of red yeast rice preparations on lipid modification (Liu J 2006). A systematic review objectively evaluating the existing evidence on the potential benefits and harms of the use of herbal medicines in HTG is needed to update the body of evidence and to help inform clinical decisions. Compared with a previous review on hyperlipidaemia (Liu J 2006), this review will focus on HTG.

**OBJECTIVES**

To assess the effects and safety of herbal medicines for hypertriglyceridaemia.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**
Randomised controlled clinical trials (RCTs) with an adequate method of random sequence generation. Adequate methods of sequence generation included computer-generated random numbers, tables of random numbers or drawing of lots. We planned to contact authors of RCTs with unclear randomisation methods to decide eligibility of the inclusion when necessary.

**Types of participants**
Adults (18 years or older) with hypertriglyceridaemia (HTG).

**Diagnostic criteria**
We included studies of participants with HTG, defined as a mean triglyceride levels greater than 2.3 mmol/L (200 mg/dL). Other definitions could be accepted because the diagnostic criteria might have changed during the last decade. We excluded trials of secondary HTG. We did not include studies of participants with borderline triglycerides levels of 150 to 199 mg/dL and participants with hypercholesterolaemia as a co-factor.

**Types of interventions**

**Intervention**
- Chinese herbal medicines (including medicines from mixtures of herbs, single herbs, Chinese proprietary medicines, or a formula of herbs prescribed by a Chinese medicine practitioner; we planned to group each category separately when conducting comparative analyses; we excluded herbal food or nutritional supplements).

*Control*
- No treatment.
- Placebo.
- Non-traditional Chinese active agents.

*Types of outcome measures*
Outcome measures sought at the end of treatment and at maximal follow-up after completion of the treatment included the following.

*Primary outcomes*
- Cardiovascular and cerebrovascular events (cardiac death, non-fatal myocardial infarction, acute coronary syndrome, coronary revascularisation (percutaneous coronary intervention and coronary artery bypass graft), transient ischaemic events (TIA), stroke (fatal and non-fatal, haemorrhagic and non-haemorrhagic)).
  - Death from any cause.
  - Serum triglyceride concentrations.

*Secondary outcomes*
- Health-related quality of life (evaluated by a validated instrument).
- Serum cholesterol levels (including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)).
- Weight, body mass index (BMI), waist-to-hip ratio (WHR).
- Adverse events (two types of adverse events were analysed, serious adverse events and adverse events not considered serious. A serious adverse event was defined as any untoward medical occurrence that resulted in death, is life-threatening, requires hospitalisation or prolongation of hospitalisations, results in persistent or significant disability/incapacity, is an event that may jeopardise the patient or requires intervention to prevent one of the former serious adverse events (ICH-GCP 1997). All other adverse events were considered non-serious).
- Costs.

*Timing of outcome measurement*
The minimum treatment duration was four weeks. We wanted to explore short-term (less than six months) and long-term (more than six months) duration in a subgroup analysis.

'Summary of findings' table
We established a ‘Summary of findings table’ reporting the following outcomes listed according to priority (Summary of findings for the main comparison).

1. Death from any cause.
2. Cardiovascular events.
3. Cerebrovascular events.
4. Adverse events.
5. Health-related quality of life.
6. Costs.
7. Serum triglyceride levels.

### Search methods for identification of studies

#### Electronic searches

We used the following sources for the identification of trials from inception to specified date.

- The Cochrane Library (2012, Issue 5)
- MEDLINE (to May, 2012)
- EMBASE (to May, 2012)
- Chinese Biomedical Database (CBM) (to May, 2012)
- China National Knowledge Infrastructure (to May, 2012)
- Chinese VIP Information (to May, 2012)
- Chinese Academic Conference Papers Database and Chinese Dissertation Database (to May, 2012)

We also searched databases of ongoing trials (http://www.controlled-trials.com/ with links to several databases and https://www.clinicaltrialsregister.eu/). We planned to provide information, including trial identifier, about recognised studies in the table ‘Characteristics of ongoing studies’. For detailed search strategies, please see under Appendix 1.

If additional key words of relevance had been detected during any of the electronic or other searches, we would have modified the electronic search strategies to incorporate these terms. We planned to include studies published in any language.

#### Searching other resources

We tried to identify additional studies by searching the reference lists of retrieved included trials and planned to scrutinise (systematic) reviews, meta-analyses, and health technology assessment reports.

#### Data collection and analysis

##### Selection of studies

To determine the studies to be assessed further, two review authors (ZLL, GQL) independently scanned the abstract, title or both sections of every record retrieved. We investigated all potentially relevant articles as full text. Where differences in opinion existed, they were resolved by a third party. If resolving disagreement had not been possible, we planned to add the article to those ‘awaiting classification’ and we planned to contact authors for clarification. We attached an adapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart of study selection (Figure 1) (Liberati 2009).
Figure 1. Study flow diagram.

1952 records identified through database searching
- EMBASE: n = 131
- MEDLINE: n = 68
- The Cochrane Library: n = 22
- CBM: n = 1344
- CNKI: n = 296
- VIP: n = 79
- Chinese Dissertation Database: n = 2
- Chinese Academic Conference Papers Database: n = 10

0 additional records identified through other sources

1875 records after duplicates removed

1875 records screened

1865 records excluded

7 full-text articles excluded
Reasons:
- No elaboration of methods of allocation sequence generation (n = 1)
- No elaboration of methods of allocation sequence generation and ineligible participants (n = 5)
- No elaboration of methods of allocation sequence generation and inclusion criteria not met (n = 1)

10 full-text articles assessed for eligibility

3 studies (3 publications) included in qualitative synthesis

0 studies (0 publications) included in quantitative synthesis (meta-analysis)
Data extraction and management

For studies that fulfilled the inclusion criteria, two review authors (ZLL, GQL) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see Characteristics of included studies; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7) with any disagreements resolved by discussion, or if required, by a third party.

We planned to send an email request to contact persons of published studies to enquire whether authors were willing to answer questions regarding their trials if required. The results of this survey are included in Appendix 8. Thereafter, we planned to seek relevant missing information on the trial from the original author(s) of the article, if required.

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary study, we wanted to maximise yield of information by simultaneous evaluation of all available data.

Assessment of risk of bias in included studies

Two review authors (ZLL, GQL) assessed each trial independently. We resolved any disagreements by consensus, or by consultation with a third party.

We assessed risk of bias using The Cochrane Collaboration’s tool (Higgins 2011). We used the following criteria.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding (performance bias and detection bias), separated for blinding of participants and personnel and blinding of outcome assessment.
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias.

We judged risk of bias criteria as 'low risk', 'high risk' or 'unclear risk' and used individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We present a 'Risk of bias' graph (Figure 2) and a 'Risk of bias' summary (Figure 3).

Figure 2. 'Risk of bias' graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

<table>
<thead>
<tr>
<th></th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data addressed</th>
<th>Free of selective reporting</th>
<th>Free of other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu 2008</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Tan 2010</td>
<td>+</td>
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<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>
We assessed the impact of individual bias domains on study results at endpoint and study levels.

**Measures of treatment effect**
We expressed dichotomous data as risk ratio (RR) with 95% confidence intervals (CI) and continuous data as differences in means (MD) with 95% CI.

**Unit of analysis issues**
We planned to take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome, if required.

**Dealing with missing data**
We performed evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat (ITT), as-treated and per-protocol (PP) populations. We investigated attrition rates, for example drop-outs, losses to follow-up and withdrawals and critically appraised issues of missing data and imputation methods (for example last-observation-carried-forward (LOCF)).

**Assessment of heterogeneity**
In the event of substantial clinical or methodological or statistical heterogeneity, we planned not to report study results as meta-analytically pooled effect estimates. We wanted to identify heterogeneity by visual inspection of the forest plots and by using a standard Chi² test with a significance level of \( \alpha = 0.1 \), in view of the low power of this test. We would have specifically examined heterogeneity employing the I² statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003), where an I² statistic of 75% and more indicated a considerable level of inconsistency (Higgins 2011). When heterogeneity was found, we planned to determine potential reasons for it by examining individual study and subgroup characteristics. We expected the following characteristics to introduce clinical heterogeneity.
- Age.
- Gender.
- Compliance.
- Comorbidity.
- Disease duration.
- Dose.
- Treatment course.
- Dosing frequency.

**Assessment of reporting biases**
Funnel plots would have been used for 10 or more studies to assess small study bias.

**Data synthesis**
We planned primarily to summarise low-risk of bias data by means of a random-effects model. We would have performed statistical analyses according to the statistical guidelines referenced in the latest version of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

**Subgroup analysis and investigation of heterogeneity**
We planned to carry out subgroup analyses of the primary outcome parameter(s) (see above) and investigate interaction. If a sufficient number of randomised trials were identified, we would have performed subgroup analyses according to formulation of herbs (extract, single herb, or mixture of herbs), and treatment duration (short-term and long-term). The following subgroup analyses were planned.
- Formulation of herbs (extract, single herb, or mixture of herbs).
- Treatment duration (no more than six months and more than six months).

**Sensitivity analysis**
We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size.
- Restricting the analysis to published studies.
- Restricting the analysis taking account risk of bias, as specified above.
- Restricting the analysis to very long or large studies to establish how much they dominate the results.
- Restricting the analysis to studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country, trials with significant skewed distributions of participants in groups (Pocock 1990).

We also wanted to test the robustness of the results by repeating the analysis using different measures of effect size (RR, odds ratio (OR), etc.) and different statistical models (fixed-effect and random-effects models).
Description of studies

Results of the search

The initial search using the electronic search strategies listed in the appendices yielded 1952 studies. Twelve unpublished studies were identified. After duplicates of different databases were removed, 1875 potentially relevant articles were kept for further assessment. After scanning the studies identified, we recognised 10 studies that could not be excluded by scrutiny of the title and abstract only. Further investigation of the full articles revealed three included studies (three included publications). Seven studies were excluded and the reasons for exclusion are listed under ‘Characteristics of excluded studies’. We prepared a PRISMA flow diagram to describe the articles found from our searches (Figure 1). No difference on the assessment on the eligibility of the studies was found between the two authors.

Missing data

There were no missing data in the three included studies.

Dealing with duplicate or companion publications

We did not find duplicate or companion documents of primary publications.

Included studies

Three randomised clinical trials (RCTs) were included in this review. Further details are given in the ‘Characteristics of included studies’ table. All trials employed a parallel two-arm design. None of the studies compared Chinese herbal medicines versus placebo. Each of the three comparisons: Chinese herbal medicines versus benz bromarone, Chinese herbal medicines plus gemfibrozil versus gemfibrozil and Chinese herbal medicines plus lifestyle intervention versus fenofibrate plus lifestyle intervention was tested in one trial, respectively. All the included studies were published studies.

Participants

One trial did not specify the diagnostic criteria (Liu 2008); the other two trials specified the diagnostic criteria of the participants in the publications (Miao 2008; Tan 2010). All three trials specified exclusion criteria. None of the included trials specified the number of screened populations. A total of 170 participants with hypertriglyceridaemia were included in the three trials; all recruited from Chinese populations. All of the randomised participants completed the study. One trial reported that the age of the participants ranged from 25 to 71 years (Miao 2008). The other two trials did not report the age range of the participants (Liu 2008; Tan 2010). One trial did not report the number of male and female participants (Tan 2010). Among the 120 participants in two trials, the proportion of males to females was 65 to 55. One trial included both inpatients and outpatients (Liu 2008). Two trials did not specify the setting (Miao 2008; Tan 2010). The pertinent patient populations of the included studies are shown in Table 1.

Interventions

In total, three different herbal medicines were tested (Table 2; Appendix 2). The formulations of all the tested herbal medicines were decoctions. Three different herbal medicines, including Zhusuan Huoxue decoction, Huoxue Huayu Tongluo decoction, and Chushi Huayu decoction, which contain Astragalus membranaceus, were evaluated in the included trials. The three formulæ each contained more than nine herbal ingredients, belonging to three classes in traditional Chinese medicine: herbs for tonifying qi, such as Astragalus membranaceus, which appeared in all three formulæ, herbs for removing dampness; such as Poria cocos, Rheum palmatum, Plantago asiatica; and herbs for promoting blood circulation, such as Salvia miltiorrhiza, Carthamus tinctorius, and Panax notoginseng.

No trial reported quality standards of the herbal preparations. The control interventions included lifestyle intervention, fenofibrate capsules, gemfibrozil tablets and benz bromarone tablets. The duration of treatment varied from four to six weeks.

Outcomes

None of the trials reported outcomes on cardiovascular and cerebrovascular events or death from any cause. Serum triglyceride levels (TG) and adverse effects were reported in all studies. Uric acid levels were reported in two studies (Liu 2008; Tan 2010). Symptoms were reported in one study (Tan 2010). Detailed information is shown in Appendix 5.

Study details

None of the three studies mentioned whether they had a run-in period and all the studies terminated as scheduled.

Publication details

Two of the three studies were published in 2008 (Liu 2008; Miao 2008) and one in 2010 (Tan 2010). All three studies were conducted in China and all were published in peer-reviewed journals in Chinese. None of the trials were claimed as commercially funded.
Excluded studies
Seven studies were excluded. They were excluded due to ineligible participants, or non-eligible interventions, or missing elaboration of methods of random sequence generation. Detailed information is shown in Characteristics of excluded studies.

Risk of bias in included studies
The trial reports provided very limited information about design and methodology. No multi-centre RCTs were identified in our searches. None of the trials reported a sample size calculation. None of the trials stated that they performed an intention-to-treat analysis, but missing data were not reported in the trials. Assessment of risk of bias is described for each included study in the Characteristics of included studies table. Review authors’ judgements about each ‘Risk of bias’ item is presented as percentages across all included studies in Figure 2, and review authors’ judgements about each ‘Risk of bias’ item for each included study is shown in Figure 3. No difference emerged on the assessment of risk of bias of the included studies between review authors.

Allocation
All the studies reported an adequate random sequence generation. Detailed information is shown in Characteristics of included studies and Figure 3.

Blinding
None of the studies reported blinding. Detailed information is shown in the Characteristics of included studies table and Figure 3.

Incomplete outcome data
Incomplete outcome data were adequately addressed in all studies. Detailed information is shown in the Characteristics of included studies table and Figure 3.

Selective reporting
None of the trials had a published protocol. According to the nominated outcomes in the methods section and the reported outcomes in the results section, we made a judgement on this domain. Two trials were free of selective reporting (Liu 2008; Tan 2010). Detailed information is shown in the Characteristics of included studies table and Figure 3.

Other potential sources of bias
We did not detect any specific type of other potential risk of bias.

Effects of interventions
See: Summary of findings for the main comparison Chinese herbal medicines for hypertriglyceridaemia

Primary Outcomes
Cardiovascular and cerebrovascular events
None of the trials reported these outcomes.

Death from any cause
None of the trials reported this outcome.

Serum triglyceride concentrations
Serum triglyceride concentrations (TG) were reported in all three studies. Compared to benz bromarone tablets, Chushihuayu decoction showed beneficial effects on lowering TG with a mean difference (MD) of -1.14 mmol/L (95% confidence interval (CI) -1.40 to -0.88; 50 participants, 1 trial; Analysis 1.1). Compared to gemfibrozil, Huoxue Huayu Tongluo decoction plus gemfibrozil did not show beneficial effects on lowering TG with a MD of -0.32 mmol/L (95% CI -0.69 to -0.05; 60 participants; 1 trial; Analysis 2.1). Compared to gemfibrozil, Huoxue Huayu Tongluo decoction plus gemfibrozil showed beneficial effects on reducing the number of patients with TG 2.2 mmol/L or more with a RR of 0.20 (95% CI 0.05 to 0.84; 60 participants, 1 trial; Analysis 2.2). Compared to fenofibrate plus lifestyle intervention, significantly higher TG levels were reported in the Zhusuan Huoxue decoction plus lifestyle intervention group with a MD of 0.51 mmol/L (95% CI 0.31 to 0.71; 60 participants; 1 trial; Analysis 3.1).

Secondary Outcomes
Health-related quality of life
None of the trials reported this outcome.

Serum cholesterol levels
None of the trials reported this outcome.

Weight, body mass index (BMI), waist-to-hip ratio (WHR)
None of the trials reported these outcomes.
Adverse events

Adverse events were observed in all three studies. Adverse reactions including gastrointestinal adverse reactions, renal colic, acute arthritis (Tan 2010), abdominal discomfort (Miao 2008) and elevated alanine-aminotransferase levels (ALT) (Liu 2008) were reported. When comparing fenofibrate plus lifestyle intervention versus Zhusun Huoxue decoction plus lifestyle intervention (Liu 2008), there was a higher number of individuals with elevated ALT (two versus zero cases, respectively - Analysis 3.2). Other comparisons also did not reveal statistically significant differences between intervention and comparator groups (Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 2.3).

Costs

None of the trials reported this outcome.

Reporting biases

We did not construct funnel plots to examine for publication and small study bias because we could not perform a meta-analysis in this systematic review. When there are fewer than 10 studies in a comparison, it is difficult to assess asymmetry by visual examination, and the power of the funnel plot test is too low to distinguish chance from real asymmetry (Higgins 2011). None of the included trials was a non-published study. None of the included trials had multiple publications.

Subgroup analyses

No subgroup analyses were done due to the limited number of trials.

Sensitivity analyses

No sensitivity analyses were done due to the limited number of trials.

Discussion

Summary of main results

Three randomised controlled trials (RCTs) with 170 participants are included in this review. The present systematic review suggests that Chinese herbal medicines used alone or in combination with other lipid-lowering drugs or lifestyle changes may have positive effects on reducing the blood levels of triglycerides (TG). However, the Chinese herbal medicine interventions did not show consistent effects on serum TG concentrations. Chushiuahu decoction showed beneficial effects on lowering TG, Huoxue Huayu Tongluo decoction plus gemfibrozil did not. Huoxue Huayu Tongluo decoction plus gemfibrozil showed beneficial effects on reducing the number of patients with a TG of 2.2 mmol/L and more, while higher TG levels were reported in the Zhusan Huoxue decoction plus lifestyle intervention group. No serious adverse events were reported. However, definite conclusions on the efficacy of Chinese herbal medicines could not be reached because of the mostly unclear risk of bias in studies and lack of reporting on patient-important and long-term outcomes.

Overall completeness and applicability of evidence

The age and gender of participants in the included trials were representative of hypertriglyceridaemic persons. All participants were recruited from Chinese populations and this could impact the applicability of the interventions to other populations. No long-term data on outcomes were reported in the included trials. Many types of Chinese herbal medicines with possible lipid-lowering effects have not been investigated in RCTs.

Quality of the evidence

All of the RCTs included in this review showed a mostly unclear risk of bias in more than one ‘Risk of bias’ domains. Study publications provided only limited descriptions of study design, allocation concealment and baseline data. No multi-centre, large scale RCTs were found. Methodologically poorly designed trials show larger differences between experimental and control groups than those conducted rigorously (Kjaergard 2001; Moher 1998; Schulz 1995). However, the insufficient number of adequate trials prohibited us from performing meaningful sensitivity analyses to show how robust the results of the review are after restricting analyses to trials with adequate methodology. Moreover, the included trials were heterogeneous in the interventions (three different herbal medicines tested only once).

Potential biases in the review process

Although we conducted comprehensive searches, we only identified and included three trials; all of them were conducted and published in Chinese. All of the trials had small sample sizes. We tried to avoid language bias and location bias, but we could not exclude potential dissemination bias. We have undertaken extensive searches for unpublished material, few of the trials identified qualified for inclusion, but at the same time we cannot disregard the fact that trials with negative findings might remain unpublished.
Agreements and disagreements with other studies or reviews

To our knowledge, no systematic review has been undertaken with a focus on Chinese herbal medicines for hypertriglyceridaemia. A systematic review on Chinese red yeast rice for dyslipidaemia was published in 2006 (Liu J 2006). This review included 93 trials with red yeast rice as the intervention and placebo as the control. Patients with primary hyperlipidaemia were included. Meta-analyses were conducted by grouping different controls and the conclusion of the review was that current evidence from randomised trials shows short-term beneficial effects of red yeast rice preparations on lipid modification (Liu J 2006). None of the trials from Liu J 2006 were included in our review. We excluded studies mostly because the participants were not patients with hypertriglyceridaemia, and therefore, did not meet our inclusion criteria. Though the two reviews did not focus on the same events, the conclusions of the review (Liu J 2006) and this review are similar as hyperlipidaemia and hypertriglyceridaemia are closely related.

AUTHORS’ CONCLUSIONS

Implications for practice

Based on this systematic review, we cannot be certain of the efficacy and safety of Chinese herbal medicines in the treatment of hypertriglyceridaemia. The evidence is inconclusive due to small number of included studies, unclear risk of bias in major domains and the inconsistency of results in the included studies.

Implications for research

For herbal mixtures, rigorous description of the pharmacology of the interventions and clinical outcomes should be emphasised. Future studies should be carried out on a formula based on our three included trials and in multiple trial centres. Standardised monitoring and reporting should be used for assessment of adverse events. Evaluation of patient-important and long-term outcomes is necessary.

ACKNOWLEDGEMENTS

We thank Ruan Yao and Wu Qiong for their contributions on this protocol. Jian Ping Liu was in part supported by grant number R24 AT001293 from the National Center for Complementary and Alternative Medicine of the US National Institutes of Health.

We thank Karla Bergerhoff of the Cochrane Metabolic and Endocrine Disorders Group for her help in the development of the search strategy.

ZLL acknowledges the support from the Australian Endeavour Award Program (Award holder number 2758 2012).

REFERENCES

References to studies included in this review

Liu 2008  [published data only]

Miao 2008  [published data only]

Tan 2010  [published data only]

References to studies excluded from this review

Cui 2005  [published data only]

Feng 2004  [published data only]

Li 2010  [published data only]

Lin 1999  [published data only]

Liu 2006  [published data only]

Chinese herbal medicines for hypertriglyceridaemia (Review)
Additional references

Anderson 2011

Barter 2006

Beltowski 2009

Chait 1992

Christian 2011

Higgins 2002

Higgins 2003

Higgins 2011

Hokanson 1996

ICH-GCP 1997

Jacobson 2009

Ji 2008

Jing 2009

Kjaergaard 2001

Kumar 2005

Le 2007

Li 2005

Liberati 2009

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Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect...
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Hebei Journal of Traditional Chinese Medicine 2007;29(9): 
807.

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Zhang SJ, Cheng ZX, Lin YW, Qin J, Cheng YH, 
Liu SL. [Efficacy of composite salviae dropping pill 
on hyperlipemia patients with phlegm and blood stasis 

Zhang 2011
sectional study on risk factors of associated type 2 diabetes 
patients among adults in Beijing. Zhonghua Liu Xing Bing 

* Indicates the major publication for the study
## Characteristics of included studies  
*ordered by study ID*

### Liu 2008

| Methods | Parallel randomised controlled clinical trial  
Comparative study design (2-sided confidence interval)  
Randomisation ratio: 1:1 |
|---|---|
| Participants | **Inclusion criteria**: primary hyperuricaemia, blood uric acid concentration > 420 mmol/L (male), > 360 mmol/L (female); TG > 117 mmol/L; age: 18 - 75 years old; participants without using uric acid-lowering drugs  
**Exclusion criteria**: acute gout episode patients; secondary hyperuricaemia patients; patients with severe primary co-morbidities on heart, liver, renal and blood systems and mental disorders  
**Diagnostic criteria**: not mentioned in the original article |
| Interventions | **Number of study centres**: 1  
**Treatment before study**: not mentioned in the original article  
**Titration period**: 4 weeks |
| Outcomes | **Outcomes reported in abstract of publication**: blood uric acid, TG |
| Study details | **Run-in period**: not mentioned in the original article  
**Study terminated before regular end**: no |
| Publication details | **Language of publication**: Chinese  
**Unclear funding**  
**Publication status**: peer review journal |
| Stated aim of study | Quote: “To investigate the clinical effectiveness and safety of Zhusuanhuoxue decoction on the patients suffered from primary hyperuricaemia combined with hypertriglyceridaemia.” |
| Notes | TG: triglycerides |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Low risk</td>
<td>Quote: &quot;Random number table was used to distribute the 60 participants to two groups”</td>
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<tr>
<td>Allocation concealment</td>
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### Liu 2008 (Continued)

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</thead>
<tbody>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Incomplete outcome data addressed             | Low risk     | Comment: no missing data         |
| All outcomes                                  |              |                                  |

| Free of selective reporting                   | Low risk     | Comment: all the prespecified outcomes in the methods section of the article were reported in the results section |

| Free of other bias                            | Unclear risk | Comment: no information on the basic characteristics of the two groups of participants and no information on funding |

### Miao 2008

<table>
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<th>Parallel randomised controlled clinical trial</th>
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<td>Randomisation ratio: 1:1</td>
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<table>
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<tbody>
<tr>
<td>Exclusion criteria: participants with severe liver or kidney diseases or hypothyroidism or drug-induced liver injury, or familial dyslipidaemia and those refused to comply with the trial</td>
<td>Exclusion criteria: not specified</td>
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<tr>
<td>Diagnostic criteria: TG ≥ 2.26 mmol/L, FBG &lt; 7mmol/L, PBG &lt; 10mmol/L; TCM differentiation: vein blood stasis syndrome</td>
<td>Diagnostic criteria: TG ≥ 2.26 mmol/L, FBG &lt; 7mmol/L, PBG &lt; 10mmol/L; TCM differentiation: vein blood stasis syndrome</td>
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<td>Study terminated before regular end: no</td>
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<tr>
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<td>Unclear funding</td>
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<tr>
<td>Publication status: peer review journal</td>
<td>Publication status: peer review journal</td>
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</table>

| Stated aim of study                           | Quote: “To investigate the clinical effectiveness and safety of Chinese integrative medicine on patients suffering from hypertriglyceridaemia with type 2 diabetes” |

| Notes                                         | FBG: fasting blood glucose; PBG: plasma blood glucose; TCM: traditional Chinese medicine; TG: triglycerides |

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### Miao 2008 (Continued)

**Risk of bias**

<table>
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<td>Comment: no information on the basic characteristics of the two group participants and no information on funding</td>
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</tbody>
</table>

**Tan 2010**

**Methods**

- Parallel randomised controlled clinical trial
- Comparative study design (2-sided confidence interval)
- Randomisation ratio: 3:2

**Participants**

- **Inclusion criteria:** not mentioned in the original article
- **Exclusion criteria:** secondary hyperuricaemia; active stage of gouty arthritis; patients with severe primary co-morbidities on heart, liver, renal and blood systems and mental disorders; age less than 18 years old; pregnant or breast feeding period; allergic condition or allergic to the tested medicine; do not meet the inclusion criteria; do not comply the trial or data missing; illegible TCM differentiation
- **Diagnostic criteria:** TG > 1.7 mmol/L; SUA > 440 mmol/L with acute gouty arthritis attack at least twice a year or SUA > 535 mmol/L without symptoms; TCM differentiation: damp and hot clip stasis

**Interventions**

- **Number of study centres:** 1
- **Treatment before study:** not mentioned in the original article
- **Titration period:** 30 days
Outcomes reported in abstract of publication: blood triglycerides, SUA and symptoms

Run-in period: not mentioned in the original article
Study terminated before regular end: no

Language of publication: Chinese
No commercial funding
Publication status: peer review journal

Quote: “To observe the clinical effects of Chushihuayu decoction on the level of serum uric acid and triglycerides in patients with hyperuricaemia and hypertriglyceridaemia”

SUA: serum uric Acid; TCM: traditional Chinese medicine; TG: triglycerides

Risk of bias

<table>
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<td>Comment: no detailed information</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Comment: no detailed information</td>
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<td>Incomplete outcome data addressed All outcomes</td>
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<td>Comment: no missing data</td>
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<td>Free of selective reporting</td>
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### Characteristics of excluded studies [ordered by study ID]

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</tr>
</thead>
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<td>Cui 2005</td>
<td>Claimed randomised clinical study without elaboration of the methods of random sequence generation. The intervention and the control group both used Chinese herbal medicines and the intervention group did not meet the inclusion criteria of this review</td>
</tr>
<tr>
<td>Feng 2004</td>
<td>Claimed randomised clinical study without elaboration of the methods of random sequence generation. The participants included hypercholesterolaemic and hypertriglyceridaemic patients and did not meet the inclusion criteria</td>
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<tr>
<td>Li 2010</td>
<td>Claimed randomised clinical study without elaboration of the methods of random sequence generation. The participants included hypercholesterolaemic and hypertriglyceridaemic patients and did not meet the inclusion criteria</td>
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<tr>
<td>Lin 1999</td>
<td>Claimed randomised clinical study without elaboration of the methods of random sequence generation. The participants included hypercholesterolaemic and hypertriglyceridaemic patients and did not meet the inclusion criteria</td>
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<tr>
<td>Liu 2006</td>
<td>Claimed randomised clinical study without elaboration of the methods of random sequence generation. The participants included hypercholesterolaemic and hypertriglyceridaemic patients and did not meet the inclusion criteria</td>
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<tr>
<td>Yang 2009</td>
<td>Claimed randomised clinical study without elaboration of the methods of random sequence generation</td>
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*Chinese herbal medicines for hypertriglyceridaemia (Review)*

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## Data and Analyses

### Comparison 1. Chushi Huayu decoction versus benzbromarone

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum triglycerides</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
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<tr>
<td>Adverse effects (total)</td>
<td>1</td>
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<td>Adverse effects (gastrointestinal)</td>
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### Comparison 2. Huoxue Huayu Tongluo decoction plus gemfibrozil versus gemfibrozil

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tr>
<td>Serum triglycerides</td>
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<td>Mean Difference (IV, Fixed, 95% CI)</td>
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### Comparison 3. Zhusuan Huoxue decoction plus lifestyle intervention versus fenofibrate capsules plus lifestyle intervention

<table>
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<th>No. of participants</th>
<th>Statistical method</th>
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</table>
Analysis 1.1. Comparison 1 Chushi Huayu decoction versus benzbromarone, Outcome 1 Serum triglycerides.

Review: Chinese herbal medicines for hypertriglyceridaemia
Comparison: 1 Chushi Huayu decoction versus benzbromarone
Outcome: 1 Serum triglycerides

<table>
<thead>
<tr>
<th>Study or subgroup</th>
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<th>Benzbromarone</th>
<th>Mean Difference</th>
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<td>Mean (SD) [mmol/L]</td>
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Favours herbs Favours benzbromarone

Analysis 1.2. Comparison 1 Chushi Huayu decoction versus benzbromarone, Outcome 2 Adverse effects (total).

Review: Chinese herbal medicines for hypertriglyceridaemia
Comparison: 1 Chushi Huayu decoction versus benzbromarone
Outcome: 2 Adverse effects (total)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
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<th>Risk Ratio</th>
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<td>n/N</td>
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<td>M-H, Fixed, 95% CI</td>
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Favours herbs Favours benzbromarone
Analysis 1.3. Comparison 1 Chushi Huayu decoction versus benzbromarone, Outcome 3 Adverse effects (gastrointestinal).

Review: Chinese herbal medicines for hypertriglyceridaemia
Comparison: Chushi Huayu decoction versus benzbromarone
Outcome: 3 Adverse effects (gastrointestinal)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Chinese herbal medicines</th>
<th>Benzbromarone</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
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<td>Tan 2010</td>
<td>1/30</td>
<td>2/20</td>
<td>0.33 [0.03, 3.44]</td>
</tr>
</tbody>
</table>

0.005 0.1 1 10 200
Favours herbs Favours benzbromarone

Analysis 1.4. Comparison 1 Chushi Huayu decoction versus benzbromarone, Outcome 4 Adverse effects (renal colic).

Review: Chinese herbal medicines for hypertriglyceridaemia
Comparison: Chushi Huayu decoction versus benzbromarone
Outcome: 4 Adverse effects (renal colic)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Chinese herbal medicines</th>
<th>Benzbromarone</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan 2010</td>
<td>0/30</td>
<td>1/20</td>
<td>0.23 [0.01, 5.28]</td>
</tr>
</tbody>
</table>

0.005 0.1 1 10 200
Favours herbs Favours benzbromarone
**Analysis 1.5. Comparison 1 Chushi Huayu decoction versus benzbromarone, Outcome 5 Adverse effect (acute arthritis).**

Review: Chinese herbal medicines for hypertriglyceridaemia

Comparison: 1 Chushi Huayu decoction versus benzbromarone

Outcome: 5 Adverse effect (acute arthritis)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Chinese herbal medicines n/N</th>
<th>Benzbromarone n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan 2010</td>
<td>0/30</td>
<td>1/20</td>
<td>0.23 [0.01, 5.28]</td>
<td>-0.002 0.1 1 10 500</td>
</tr>
</tbody>
</table>

Favours herbs        Favours benzbromarone

---

**Analysis 2.1. Comparison 2 Huoxue Huayu Tongluo decoction plus gemfibrozil versus gemfibrozil, Outcome 1 Serum triglycerides.**

Review: Chinese herbal medicines for hypertriglyceridaemia

Comparison: 2 Huoxue Huayu Tongluo decoction plus gemfibrozil versus gemfibrozil

Outcome: 1 Serum triglycerides

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Herbs+gemfibrozil N Mean(SD)[mmol/L]</th>
<th>Gemfibrozil N Mean(SD)[mmol/L]</th>
<th>Mean Difference IV,Fixed 95% CI</th>
<th>Mean Difference IV,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miao 2008</td>
<td>30 1.79 (0.68)</td>
<td>30 2.11 (0.77)</td>
<td>-0.32 [-0.69, 0.05]</td>
<td>-1 -0.5 0 0.5 1</td>
</tr>
</tbody>
</table>

Favours herbs+gemfibrozil        Favours gemfibrozil

---

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**Analysis 2.2. Comparison 2 Huoxue Huayu Tongluo decoction plus gemfibrozil versus gemfibrozil, Outcome 2 Number of patients with triglycerides $\geq 2.2$ mmol/L.**

Review: Chinese herbal medicines for hypertriglyceridaemia

Comparison: 2 Huoxue Huayu Tongluo decoction plus gemfibrozil versus gemfibrozil

Outcome: 2 Number of patients with triglycerides $\geq 2.2$ mmol/L

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Herbs+gemfibrozil</th>
<th>Gemfibrozil</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miao 2008</td>
<td>2/30</td>
<td>10/30</td>
<td>0.20 [0.05, 0.84]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Favours herbs+gemfibrozil</td>
</tr>
</tbody>
</table>

**Analysis 2.3. Comparison 2 Huoxue Huayu Tongluo decoction plus gemfibrozil versus gemfibrozil, Outcome 3 Adverse effects (stomachache).**

Review: Chinese herbal medicines for hypertriglyceridaemia

Comparison: 2 Huoxue Huayu Tongluo decoction plus gemfibrozil versus gemfibrozil

Outcome: 3 Adverse effects (stomachache)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Herbs+gemfibrozil</th>
<th>Gemfibrozil</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu 2008</td>
<td>2/30</td>
<td>10/30</td>
<td>0.20 [0.05, 0.84]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Favours herbs+gemfibrozil</td>
</tr>
</tbody>
</table>
Analysis 3.1. Comparison 3 Zhusuan Huoxue decoction plus lifestyle intervention versus fenofibrate capsules plus lifestyle intervention, Outcome 1 Serum triglycerides.

Review: Chinese herbal medicines for hypertriglyceridaemia

Comparison: 3 Zhusuan Huoxue decoction plus lifestyle intervention versus fenofibrate capsules plus lifestyle intervention

Outcome: 1 Serum triglycerides

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Chinese herbal medicines</th>
<th>Fenoﬁbrate</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)[mmol/L]</td>
<td>N Mean(SD)[mmol/L]</td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Liu 2008</td>
<td>30 2.262 (0.44)</td>
<td>30 1.75 (0.35)</td>
<td>0.51 [0.31, 0.71]</td>
<td></td>
</tr>
</tbody>
</table>

-2 -1 0 1 2
Favours herbs Favours fenofibrate

Analysis 3.2. Comparison 3 Zhusuan Huoxue decoction plus lifestyle intervention versus fenofibrate capsules plus lifestyle intervention, Outcome 2 Adverse effect (elevated ALT).

Review: Chinese herbal medicines for hypertriglyceridaemia

Comparison: 3 Zhusuan Huoxue decoction plus lifestyle intervention versus fenofibrate capsules plus lifestyle intervention

Outcome: 2 Adverse effect (elevated ALT)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Chinese herbal medicines</th>
<th>Fenoﬁbrate</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Liu 2008</td>
<td>0/30</td>
<td>2/30</td>
<td>0.20 [0.01, 4.00]</td>
<td></td>
</tr>
</tbody>
</table>

0.001 0.01 0.1 1 10 100 1000
Favours herbs Favours fenofibrate

Chinese herbal medicines for hypertriglyceridaemia (Review)

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### Table 1. Overview of study populations

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Intervention(s) and comparator(s)</th>
<th>[N] screened / eligible</th>
<th>[N] randomised</th>
<th>[N] safety</th>
<th>[N] ITT study</th>
<th>[N] finishing study</th>
<th>[%] of randomised participants finishing study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liu 2008</strong></td>
<td>Zhusuan Huoxue decoction plus lifestyle intervention</td>
<td>-</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Fenofibrate&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>30</td>
<td>30</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>total:</td>
<td></td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td><strong>Miao 2008</strong></td>
<td>Huoxue Huayu Tongluo decoction plus gemfibrozil</td>
<td>-</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Gemfibrozil&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
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<td>30</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td></td>
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<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td><strong>Tan 2010</strong></td>
<td>Chushi Huayu decoction</td>
<td>-</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Benzbromarone&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
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<td>20</td>
<td>100</td>
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<tr>
<td></td>
<td>total:</td>
<td></td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>All interventions</strong></td>
<td></td>
<td>90</td>
<td></td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>All comparators</strong></td>
<td></td>
<td>80</td>
<td></td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>All interventions and comparators</strong></td>
<td></td>
<td>170</td>
<td></td>
<td>170</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Denotes not reported

<sup>a</sup>Fenofibrate: a cholesterol-lowering drug belonging to the fibric acid derivatives group

<sup>b</sup>Gemfibrozil: a triglycerides-lowering drug belonging to the fibric acid derivatives group

<sup>c</sup>Benzbromarone: a potent uricosuric agent for treatment of gout introduced in the 1970 but also used as a triglycerides lowering drug

ITT: intention-to-treat
Table 2. Chinese herbal medicines and their ingredients

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Chinese formula</th>
<th>Botanical name of ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan 2010</td>
<td>Chushi Huayu decoction</td>
<td><em>Smilax glabra</em>, <em>Dioscorea hypoglauca</em>, <em>Coix lacryma-jobi var. ma-yuen</em>, <em>Leonurus heterophylus</em>, <em>Lysimachia christinae</em>, <em>Plantago asiatica</em>, <em>Saliva miltorrhiza</em>, <em>Astragalus membranaceous</em>, <em>Rheum palmatum</em>, <em>Glycyrrhiza uralensis</em>.</td>
</tr>
</tbody>
</table>

**APPENDICES**

Appendix 1. Search strategies

**Search terms**

Unless otherwise stated, search terms are free text terms. Abbreviations:

'S': stands for any character; '?' substitutes one or no character; adj: adjacent (i.e. number of words within range of search term); exp: exploded MeSH; MeSH: medical subject heading (MEDLINE medical index term); pt: publication type; sh: MeSH; tw: text word

The Cochrane Library

#1 MeSH descriptor Hypertriglyceridaemia explode all trees
#2 (hypertriglyceridaemia* in All Text or hypertriglyceridaemia* in All Text or hypertriglyceridaemia* in All Text or hypertriglyceridaemia* in All Text)
#3 (#1 or #2)
#4 MeSH descriptor Drugs, Chinese herbal explode all trees
#5 MeSH descriptor Phytotherapy explode all trees
#6 MeSH descriptor Herbal medicine explode all trees
MEDLINE

1 exp Hypertriglyceridaemia/
3 1 or 2
4 exp Drugs, Chinese Herbal/
5 exp Phytotherapy/
6 exp Herbal Medicine/
7 exp Plants, Medicinal/
8 exp Plant Preparations/
9 exp Plant Extracts/
10 exp Medicine, Kampo/
11 exp Medicine, Chinese traditional/
12 ((herbal adj6 (remed* or extract* or preparation* or mixture* or medic*)).tw,ot.
13 (phyto adj6 (drug* or pharmaceutical* or therap* or treatment* or medic*)).tw,ot.
14 ((Chinese adj6 (herb* or plant* or medic* or drug* or formul* or prescri*)).tw,ot.
15 (plant* adj6 (preparation* or extract* or medic*)).tw,ot.
16 ((Chinese adj6 traditional medic*)).tw,ot.
17 botanical extract*.tw,ot.
18 ox/4-17
19 3 and 18
20 (animals not (humans and animals)).sh.
21 19 not 20

EMBASE

1 exp hypertriglyceridaemia/
3 1 or 2
4 exp medicinal plant/ or exp plant extract/ or exp Chinese drug/ or exp Chinese herb/ or exp herbaceous agent/ or exp Chinese medicine/ or exp herbal medicine/

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5 exp phytotherapy/
6 (herbal adj6 (remed* or extract* or preparation* or mixture* or medic*)).tw,ot.
7 (phyto adj6 (drug* or pharmaceutical* or therap* or treatment* or medic*)).tw,ot.
8 (Chinese adj6 (herb* or plant* or medic* or drug* or formul* or prescri*)).tw,ot.
9 (plant* adj6 (preparation* or extract* or medic*)).tw,ot.
10 (Chinese adj6 traditional medic*).tw,ot.
11 botanical extract*.tw,ot.
12 or/4-11
13 3 and 12
14 limit 13 to human

### Chinese BioMedical Database

1 MeSH ="hypertriglyceridaemia /all subtitles/all trees"
2 MeSH ="hyperlipoproteinemias/all subtitles/all trees"
3 hypertriglyceridaemia
4 MeSH="triglyceride /BL/all trees"
5 triglyceride ascend
6 hyperlipoproteinemias
7 MeSH="medicine, eastern tradition/all subtitles/all trees"
8 MeSH="complementary medicine/"
9 MeSH="plant extracts/all subtitles/all trees"
10 MeSH="Plant, Therapeutic Use /All subtitles"
11 MeSH="drugs, over the counter"
12 MeSH="Phytotherapy/All subtitles/all trees"
13 Herbs or herbal or herb
14 Alternative medicine*
15 Complementary medicine*
16 Traditional medicine*
17 plant or plants
18 (China or The East) with medicine*
19 Plant medicinal product * or medicinal materials or herbal medicine
20 Chinese herbal drugs * or Chinese medicine*
21 Traditional Chinese Medicine *
22 Traditional Chinese Medicine and Western Medicine*
23 MeSH="animals/all trees"
24 not #23
25 MeSH="Chinese herbal drugs/all subtitles"
26 #6 or #5 or #4 or #3 or #2 or #1
27 #25 or #22 or #21 or #20 or #19 or #18 or #17 or #16 or #15 or #14 or #13 or #12 or #11 or #10 or #9 or #8 or #7
28 #27 and #26 and #24
29 Title: rats or rabbits
30 (not #29) and #28
31 #30 and (summary in MH or summary in PT)
32 (not #31) and #30

### China National Knowledge Infrastructure
1 triglyceride ascend or high triglyceride or hypertriglyceridaemia or hyperlipidaemia
2 Chinese herbal medicine or Chinese medicine or Chinese and western or plants or herbs
3 1 and 2

Chinese VIP Information

1 triglyceride ascend or high triglyceride or hypertriglyceridaemia or hyperlipidaemia
2 Chinese herbal medicine or Chinese medicine or Chinese and western or plants or herbs
3 1 and 2

Chinese Academic Conference Papers Database and Chinese Dissertation Database

hypertriglyceridaemia and (Chinese medicine or Chinese herbal medicine or Chinese and Western or plants or herbs) and randomizations

Appendix 2. Description of interventions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention(s) [route, frequency, total dose/day]</th>
<th>Comparator(s) [route, frequency, total dose/day]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study ID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu 2008</td>
<td>Zhusuan Huoxue decoction plus lifestyle intervention (oral, twice daily)</td>
<td>Fenofibrate capsules plus lifestyle intervention (oral, once daily, 0.2 g/day)</td>
</tr>
<tr>
<td>Miao 2008</td>
<td>Huoxue Huayu Tongluo decoction (oral, twice daily, 300 mL/day) plus gemfibrozil (oral, twice daily, 0.4 g/day)</td>
<td>Gemfibrozil tablets (oral, twice daily, 0.4 g/day)</td>
</tr>
<tr>
<td>Tan 2010</td>
<td>Chushi Huayu decoction, oral, twice/day, 400 mL/day, one dose/day</td>
<td>Benz bromarone tablets, oral, once/day, 50 mg/day</td>
</tr>
</tbody>
</table>

Appendix 3. Baseline characteristics (I)

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Intervention(s) and comparator(s)</th>
<th>Duration of intervention</th>
<th>Duration of follow-up</th>
<th>Participating population</th>
<th>Country</th>
<th>Setting</th>
<th>Ethnic groups [%]</th>
<th>Duration of disorder [mean years (SD)/range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu 2008</td>
<td>Zhusuan Huoxue decoction plus lifestyle intervention</td>
<td>4 weeks</td>
<td>No follow-up</td>
<td>Participants with hypertriglyceridaemia and China</td>
<td>in- and out-patients</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

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## Appendix 4. Baseline characteristics (II)

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Intervention(s) and comparator(s)</th>
<th>Sex [female %]</th>
<th>Age [mean (SD)]</th>
<th>BMI [mean (SD)]</th>
<th>Co-medications / Co-interventions</th>
<th>Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu 2008</td>
<td>Zhusuan Huoxue decocion plus lifestyle intervention</td>
<td>20</td>
<td>60 (13)</td>
<td>-</td>
<td>Lifestyle intervention</td>
<td>Hyperuricaemia</td>
</tr>
<tr>
<td></td>
<td>Fenofibrate capsules plus lifestyle intervention</td>
<td>13</td>
<td>60 (11)</td>
<td>-</td>
<td>Lifestyle intervention</td>
<td>Hyperuricaemia</td>
</tr>
</tbody>
</table>

Footnotes

"-" denotes not reported
SD: standard deviation
## Appendix 5. Matrix of study endpoints (publications)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study ID</th>
<th>Primary endpoint(s)*</th>
<th>Secondary endpoint(s)*</th>
<th>Other endpoint(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[time of measurement]</td>
<td>[time of measurement]</td>
<td>[time of measurement]</td>
</tr>
<tr>
<td>Liu 2008</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Uric acid (0, 4 wk), triglycerides (0, 4 wk), adverse effects (0, 4 wk)</td>
</tr>
<tr>
<td>Miao 2008</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Triglycerides (-1, 7 wk), adverse effects (-1, 7 wk)</td>
</tr>
<tr>
<td>Tan 2010</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Symptoms (0, 30 d), uric acid (0, 30 d), triglycerides (0, 4 wk), adverse effects (0, 30 d)</td>
</tr>
</tbody>
</table>

*“-” denotes not reported; BMI: body mass index; SD: standard deviation
**Footnotes**

*a* Primary or secondary endpoint(s) refer to verbatim statements in the publication, other endpoints relate to outcomes which were not specified as 'primary' or 'secondary' outcomes in the publication

"-" denotes not reported;
d: days; wk: weeks

### Appendix 6. Adverse events (I)

<table>
<thead>
<tr>
<th>Characteristic Study ID</th>
<th>Intervention(s) and comparator(s)</th>
<th>Deaths [n/N]</th>
<th>All adverse events [n/N (%)]</th>
<th>Severe/serious adverse events [n/N (%)]</th>
<th>Drop-outs due to adverse events [n/N (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liu 2008</strong></td>
<td>Zhusuan Huoxue decoction plus lifestyle intervention</td>
<td>0/30</td>
<td>0/30</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td></td>
<td>Fenofibrate capsules plus lifestyle intervention</td>
<td>0/30</td>
<td>2/30 (6.7)</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td></td>
<td>all:</td>
<td>0/60</td>
<td>2/60 (3.3)</td>
<td>0/60</td>
<td>0/60</td>
</tr>
<tr>
<td><strong>Miao 2008</strong></td>
<td>Huoxue Huayu Tongluo decoction plus gemfibrozil</td>
<td>0/30</td>
<td>0/30</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td></td>
<td>Gemfibrozil tablets</td>
<td>0/30</td>
<td>3/30 (10.0)</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td></td>
<td>all:</td>
<td>0/60</td>
<td>3/60 (5.0)</td>
<td>0/60</td>
<td>0/60</td>
</tr>
<tr>
<td><strong>Tan 2010</strong></td>
<td>Chushi Huayu decoction</td>
<td>0/30</td>
<td>1/30 (3.3)</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td></td>
<td>Benzbromarone tablets</td>
<td>0/20</td>
<td>4/20 (20.0)</td>
<td>0/20</td>
<td>0/20</td>
</tr>
<tr>
<td></td>
<td>all:</td>
<td>0/50</td>
<td>5/50 (10.0)</td>
<td>0/50</td>
<td>0/50</td>
</tr>
</tbody>
</table>
### Appendix 7. Adverse events (II)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study ID</th>
<th>Intervention(s) and comparator(s)</th>
<th>Hospitalisation [n/N (%)]</th>
<th>Out-patient treatment [n/N (%)]</th>
<th>Symptoms [n/N (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liu 2008</td>
<td>Zhusuan Huoxue decoction plus lifestyle intervention</td>
<td>0/30</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fenofibrate capsules plus lifestyle intervention</td>
<td>0/30</td>
<td>0/30</td>
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<tr>
<td></td>
<td></td>
<td>all:</td>
<td>0/60</td>
<td>0/60</td>
<td>0/60</td>
</tr>
<tr>
<td></td>
<td>Miao 2008</td>
<td>Huoxue Huayu Tongluo decoction plus gemfibrozil</td>
<td>0/30</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemfibrozil tablets</td>
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<td>-</td>
<td>3/30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all:</td>
<td>0/60</td>
<td>-</td>
<td>3/60</td>
</tr>
<tr>
<td></td>
<td>Tan 2010</td>
<td>Chushi Huayu decoction</td>
<td>0/30</td>
<td>0/30</td>
<td>1/30 (3.3)</td>
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<td></td>
<td>Benzbromarone tablets</td>
<td>0/20</td>
<td>0/20</td>
<td>4/20 (20.0)</td>
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<tr>
<td></td>
<td></td>
<td>all:</td>
<td>0/50</td>
<td>0/50</td>
<td>5/50 (10.0)</td>
</tr>
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</table>

*Footnotes*

“-“ denotes not reported

### Appendix 8. Survey of authors providing information on included trials

<table>
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<tr>
<th>Characteristic</th>
<th>Study ID</th>
<th>Study author contacted</th>
<th>Study author replied</th>
<th>Study author provided data</th>
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<td></td>
<td>Liu 2008</td>
<td>Y</td>
<td>Y (author’s email: <a href="mailto:doctorabcde@163.com">doctorabcde@163.com</a>)</td>
<td>The detailed compositions of Zhusuan Huoxue decoction were:</td>
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</table>
CONTRIBUTIONS OF AUTHORS

Zhao Lan Liu (ZLL): protocol draft, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and update draft.

George Qian Li (GQL): protocol draft, search strategy development, trial selection, data extraction, data analysis, data interpretation and update draft.

Alan Bensoussan (LB): protocol draft, data interpretation and update draft.

Hosen Kiat (HK): protocol draft, review draft and update draft.

Kelvin Chan (KC): data interpretation and update draft.

Jian Ping Liu (JPL): protocol draft, search strategy development, trial selection, data extraction, data analysis, data interpretation, review draft and update draft.

DECLARATIONS OF INTEREST

None known.

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External sources
- Grant number 2011ZX09302-006 from the Ministry of Science and Technology, China.
- Grant number JYBZZ-JS006 from Beijing University of Chinese Medicine, China.
- Grant number CSO-51 from Global fund for HIV, China.
DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Review authors have changed since the published protocol. One review author (Qiong Wu) was removed and one review author (Kelvin Chan) was added.

INDEX TERMS

Medical Subject Headings (MeSH)
Drugs, Chinese Herbal [*therapeutic use]; Gemfibrozil [therapeutic use]; Hypertriglyceridemia [*drug therapy]; Hypolipidemic Agents [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words
Humans